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## REMARKS

### 1 PRELIMINARY

Applicant acknowledges the withdrawal of claims 1-15 and 24-60 pursuant to 37 C.F.R. § 1.142(b). Applicant requests cancellation of these claims without prejudice or disclaimer to the subject matter contained therein. Claims 16-23 are pending in the instant application; claims 16, 18 and 22 are independent.

Support for the amendment to the claims and the correction of the specification is found throughout the application as filed. In particular, support is found in Table 1, wherein the chemical structure of exemplary oligonucleotides of the invention is provided, demonstrating that 7 nucleosides 5' to the CpG motif and 10 nucleosides 3' to the CpG motif are contemplated for substitution. Support for the amendment to Example 2 of the application is found in the priority document U.S. provisional application serial number 60/178,562. Amendment of the drawings is supported by the application as filed. Figure 1 has been simplified byremoving data not relied on herein. Figure 2 has been deleted, and Figure 3 is now renumbered as Figure 2. The amendments submitted herewith adds no new matter.

### 2 OBJECTIONS

The specification has been objected to because Example 2 refers to a mouse spleen cell proliferation assay described in Example 1, but this example provides no such description.

Applicant regrets the clerical error. Applicant has submitted herewith an amendment to correct this clerical error. After entry of the amendment, the application provides the description of the assay found in the priority document U.S. provisional application serial number 60/178,562.

### 3 REJECTIONS

#### A) The Rejection of Claims 16-23 Under 35 U.S.C. § 112, Second Paragraph

Claims 16-23 are rejected under 35 U.S.C. § 112, second paragraph. The Office Action states that "4th nucleosidc 3' to the CpG dinucleotide" is repeated several times and appropriate clarification is required.

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Independent claims 16, 18 and 22 are amended herewith to more clearly recite Applicant's invention. Applicant regrets the confusion and thanks the Examiner for the opportunity to correct this clerical error.

The Office Action also states that the metes and bounds of the term "increasing the immunostimulatory effect" in claim 16, line 1, and of the term "having increased [immuno]stimulatory effects" in claim 18, lines 1-2, are vague and unclear. Applicant traverses the rejection on this basis.

Applicant asserts that the plain meaning of the terms "increasing" or "increased" is intended. One skilled on the art would know that the terms simply refer to any increase in a measured value. Applicant's specification teaches methods of measuring "immunostimulatory effects." More specifically, the specification teaches in Example 2 a method of measuring *in vitro* immunostimulatory effects utilizing a mouse spleen cell proliferation assay. The specification also teaches in Example 3 a method of measuring immunostimulatory effects *in vivo* by determining the extent of spleenomegaly after the administration of an oligonucleotide.

In view of Applicant's amendment and remarks, withdrawal of the outstanding rejections is respectfully requested.

**B) The Rejection of Claims 16-23 Under 35 U.S.C. § 112, First Paragraph**

The Office Action rejects claims 16-23 under 35 U.S.C. § 112, first paragraph, stating that the specification does not reasonably provide enablement for compositions and methods for increasing the immunostimulatory effects *in vitro* and *in vivo* in any and/or all organisms comprising the administration of 3'-substituted CpG containing oligonucleotides, whereby the 3' substitutions occur between 3-6 nucleosides 5' from the CpG dinucleotide or 2-6 nucleosides 3' of the CpG dinucleotide. The Office Action states that the specification is enabling for a method of increasing mouse spleen cell proliferation *in vitro* and *in vivo* comprising the administration of 3'-O-methylribonucleoside, 2'-5' methyl phosphonate internucleotide-containing CpG oligonucleotides, whereby the 3'-O-methylribonucleosides are located 3 or 4 nucleosides 5' to the CpG dinucleotide. Applicant respectfully traverses this rejection.

Applicant avers that the specification is enabling for the scope of the pending claims. In *In re Goffe*, 542 F.2d 564, 191 USPQ 429, 431 (CCPA 1976), the court stated,

> "[T]o provide effective incentives, claims must adequately protect inventors. To demand that the first to disclose shall limit

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> his claims to what has found will work or to materials which meet the guidelines specified for "preferred" materials in a process such as the one herein involved would not serve the constitutional purpose of promoting progress in the useful arts."

Thus, an Applicant should not be required to disclose all possible embodiments of an invention. As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. § 112 is satisfied. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Failure to disclose other methods by which the claimed invention may be made does not render a claim invalid under 35 U.S.C. § 112. Spectra-*Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524, 1533, 3 USPQ2d 1737, 1743 (Fed. Cir.), cert. denied, 484 U.S. 954 (1987).

Applicant's specification teaches that when nucleosides in a CpG containing oligonucleotide are substituted with modified nucleosides, the immunostimulatory effects of the substituted oligonucleotide increases or decreases relative to the activity of the parent oligonucleotide. Applicant's specification teaches methods to measure immunostimulatory effects *in vitro* (Example 2) and *in vivo* (Example 3). The mouse model system utilized by these assays is an art-recognized model system for studying immune responses.

The Office Action comments on the state of the prior art and the predictability or unpredictability of the art. The Office Action cites McCluskie *et al.* as indicating that the biological effects to the administration of CpG containing oligonucleotides varies depending on the mode of administration. However, Applicant does not believe that McCluskie *et al.* is prior art. The cited reference provides some background information related to DNA-based vaccines and the role that CpG dinucleotides play in immune response induction. McCluskie *et al.* is really about DNA vaccination with recombinant plasmids. Plasmids are typically at least several thousand base pairs in length, and the cellular uptake of DNA of this size is not predicted to be the same to that of an oligonucleotide. Moreover, the immune response measured in McCluskie *et al.* is dependent upon multiple factors that are not relevant to the use of CpG-containing oligonucleotides: (1) the plasmid must be introduced into a target cell (uptake is expected to be different than with an oligo), (2) efficient transcription of the antigen-encoding DNA sequence must occur, (3) the antigen-encoding RNA must be efficiently translated, (4) the expressed antigen must have a sufficient half-life to be useful for the induction of an immune response, and (6) the expressed antigen must be sufficiently antigenic to provide a strong immune response.

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Thus, any of these factors can influence the efficiency of the immune response, the variations in immune response dependent upon mode of delivery and the predictive value of the mouse model system for this type of vaccination. In fact the Office Action cites page 296, which details these variables and others that point to the inapplicability of this reference to the present invention.

The Office Action also cites Krieg *et al.*, particularly page 524, as indicating that the biological effects to the administration of CpG containing oligonucleotides varies depending on the mode of administration. Applicant strongly disagrees. Inspection of page 524 indicates the opposite. In the first full paragraph on page 524, Krieg et al. state: "[t]hese and subsequent studies have shown that CpG DNA to be a more effective Th1-like adjuvant than complete Freund's, and to be effective with multiple types of antigens and routes of administration, including mucosal immunization (reviewed in Ref. 50)." Krieg *et al.* further state in this paragraph that "[u]nlike many vaccine adjuvants that have been extremely effective in mice but disappointing in humans, CpG DNA is also highly effective in higher primates (citations omitted)." Thus, Krieg *et al.* actually supports the notion that modes of administration is not a variable for the generation of a CpG-mediated immune response, and the reference also validates the use of the mouse as a model system for the study of CpG-mediate immune response effects.

The Office Action cites Weiner as indicating that the molecular mechanisms of CpG oligonucleotides' immunostimulatory effects are not yet understood. In response, Applicant points out that it is not necessary for Applicant to understand how the invention works; the fact that the specification teaches the invention is sufficient for patentability.

The Office Action cites Agrawal *et al.*, particularly pages 78-80, and the instant specification, pages 31-32, as indicating the incorporation and positioning of chemical modifications relative to the positioning of the CpG dinucleotide are highly unpredictable. The Agrawal *et al.* reference is a review on antisense therapeutics. CpG dinucleotides are mentioned in the cited pages in the context of reducing these sequences to minimize non-antisense related effects in the administration of antisense oligonucleotides. Agrawal *et al.* does teach modifications of oligonucleotides to improve, for example, stability. Moreover, the cited reference concludes that "... it is becoming clear that antisense oligonucleotide therapeutics can in fact be as simple as complementary base recognition, but only if proper design precautions and controls are used." Obviously, Agrawal *et al.* teach those design precautions and controls, some of which are undoubtedly applicable to CpG oligonucleotide immune therapeutics.

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The Office Action states that Applicant has not provided guidance in the specification commensurate with the scope of the claims. Applicant disagrees. Applicant's specification teaches the synthesis of modified CpG-containing oligonucleotides. The specification also teaches testing the immunostimulatory properties of modified oligonucleotides *in vitro* (Example 2) and *in vivo* (Example 3).

Applicant also disagrees with the statement in the Office Action that it would require undue experimentation to practice claimed invention. Applicant holds that the specification teaches the synthesis of modified oligonucleotides and *in vitro* and *in vivo* testing of the immunostimulatory properties of the claimed oligonucleotides. One skilled in the art would clearly be able to practice the invention without undue experimentation.

Applicant respectfully requests withdrawal of the outstanding rejection.

**C) The Rejection of Claims 18, 20 and 21 Under 35 U.S.C. § 102(b)**

The Office Action rejects claims 18, 20 and 21 under 35 U.S.C. § 102(b) as being unpatentable in view of U.S. patent number 5,801,154 to Baracchini *et al.* (hereinafter the '154 patent). Applicant traverses this rejection.

A proper reference under 35 U.S.C. § 102 must place the invention into the hands of the skilled artisan. It must meet the "description" and "enabling disclosure" requirements of 35 U.S.C. § 112. This is the minimum qualitative level that a reference must meet. *In re Hoeksema*, 399 F.2d 269, 273, 158 USPQ 596, 600 (CCPA 1968); *In re LeGrice*, 301 F.2d 929, 936, 133 USPQ 365, 372 (CCPA 1962). Moreover, "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

Applicant asserts that the '154 patent is not anticipatory. The cited patent provides no indication of a CpG-cotaining oligonucleotide having "increased immunostimulatory effect." The Office Action assumes that the CpG-containing oligonucleotides described in the '154 patent are immunostimulatory, but there is no evidence to sustain such an assertion. Also, the '154 patent is not an enabling reference. It provides no teaching on the measurement of immunostimulatory effects *in vitro* or *in vivo*.

In view of the remarks provided herewith, Applicant respectfully requests withdrawal of the outstanding rejection.

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## CONCLUSIONS

It is believed that all of the objections and rejections raised in the outstanding Office Action have been addressed, and the amendment and remarks provided herewith have resolved all out-standing issues in the prosecution of the captioned application. Applicants respectfully request allowance of the currently pending claims.

No additional fees are believed to be due in connection with this communication. However, please apply any additional charges, or credit any overpayment, to Deposit Account No. 50-2285. If the Examiner is of the opinion that a telephone conference would expedite prosecution of the captioned application, the Examiner is encouraged to contact Applicants' undersigned representative.

Respectfully submitted,

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